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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR THE RESPONDENTS

OPINIONS BELOW

The opinion of the court of appeals (A. 466–473) is reported at 461 F. 2d 223. The opinion of the district court (A. 463–466) is not yet reported.[1]

JURISDICTION

The judgment of the court of appeals (A. 474) was entered on May 24, 1972. A petition for rehearing was denied on July 5, 1972. The Chief Justice extended the time within which to file a petition for a writ of certiorari until October 30, 1972. The petition was filed

[1] The district court's opinion appears at CCH Food, Drug, and Cosmetic L. Rep. ¶ 40,489.

on that date, and was granted on January 8, 1973. The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

QUESTIONS PRESENTED

Whether Section 107(c)(4) of the Drug Amendments of 1962 exempts from the Amendments' drug effectiveness requirements—

1. Certain categories of ineffective drug products with respect to which a new drug application was on file with the Food and Drug Administration at the time the 1962 Amendments went into effect.

2. Ineffective drug products marketed prior to the 1962 Amendments without an application on file, but which are identical or substantially similar to products for which an application was effective.

STATUTES INVOLVED

Pertinent provisions of Sections 201(p) and 505 of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1040, are reproduced at A. 482–484. These provisions, as amended by the Drug Amendments of 1962, 76 Stat. 780, 788–789, are set forth at A. 475–481.

Section 107(c) of the Drug Amendments of 1962, 76 Stat. 788–789, note following 21 U.S.C. 321, provides:

> SEC. 107(c)(1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.
>
> (2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be

deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until

whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

STATEMENT

This is one of five interrelated cases pending before the Court on writs of certiorari involving the Drug Amendments of 1962, P.L. 87–781, 76 Stat. 780 *et seq.*, which amended the definition of "new drug" in Section 201(p) of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1040 *et seq.*, to include the concept of drug effectiveness, and which added a requirement for drug effectiveness to the provisions for administrative clearance and supervision of drugs contained in Section 505 of the Act.[2] A back-

[2] The other cases are: *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394; *Hynson, Westcott and Dunning, Inc.* v. *Weinberger*, No. 72–414 (cross-petition); *CIBA Corporation* v. *Weinberger*, No. 72–528; and *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555.

ground statement describing the general history and operation of the statutes involved is set forth at pp. 3–25 of the government's brief in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555 (the "*Bentex* case"). We respectfully refer the Court to that statement for purposes of this case as well.

Briefly, the 1938 Act provided in Section 505, 52 Stat. 1052 (A. 483) for a system of administrative pre-marketing clearance and subsequent administrative supervision of any "new drug." Such a drug was defined as any drug not generally recognized by qualified experts as safe for its intended use. Section 201(p)(1), 52 Stat. 1041, 1042. A new drug could not lawfully be marketed unless there was effective with respect to it a "new drug application" ("NDA") filed with the Food and Drug Administration to establish its safety for use. Section 505(a) (A. 483).

In the Drug Amendments of 1962, Congress modified these provisions by adding the further requirement that drugs be demonstrated to be effective, as well as safe, for their intended use. In Section 107(a), 76 Stat. 788, Congress provided that the 1962 Amendments should take effect on the date of enactment, October 10, 1962, except as otherwise provided. In Section 107(c), the Amendments set forth specific provisions governing the application of the new "effectiveness" standard to drugs already being marketed when the 1962 Amendments took effect. This case involves the interpretation of these transition provisions.

Petitioner sells a line of drugs containing citrus bioflavonoid as a principal active ingredient (A. 276).

Bioflavonoids are chemicals extracted from fruit skins (A. 371). When used in the dosage recommended for petitioner's products, they are not pharmacologically toxic in the sense that a normal individual would develop adverse reactions from them (A. 370–371).

All of petitioner's products contain the identical citrus bioflavonoid compound. New drug applications for petitioner's products became effective as follows (A. 368):

	Effective date
NDA 9965:	
CVP Capsules	Nov. 8, 1955
CVP Syrup	Nov. 8, 1955
CVP with Vitamin K Syrup	Nov. 8, 1955
(Supplement):	
CVP with Vitamin K Tablets	Jan. 19, 1956
Duo-CVP Capsules	
NDA 11474: Prednyl	[3] Aug. 26, 1956
NDA 11475: Prednis-CVP	Aug. 26, 1956

No NDA was ever filed with respect to "Duo-C.V.P. with Vitamin K Capsules" or "Bivam" (A. 368).

On April 19, 1961, the Director of the New Drug Branch of the Bureau of Medicine in the Food and Drug Administration advised petitioner that two of these products, Prednyl and Prednis-CVP, were not, "[i] our opinion * * * new drugs when distributed under the labeling provided for in the respective new drug applications" (A. 300, 369). That labeling recommended use of the drugs in the treatment of capillary fragility and permeability occurring in various conditions. The Director declined to comment on the status of other products because the final printed labeling for

[3] Prednyl was no longer marketed in the United States when the Drug Amendments of 1962 became effective (A. 368).

them was not on file with the agency (A. 300).[4] On May 16, 1961, petitioner submitted the labeling and stated that "[i]t is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective" (App. 301). FDA did not respond to that letter.

Petitioner's C.V.P. products were described in its labeling as a water-soluble biologically active flavonoid compound made from citrus peel and pulp combined with ascorbic acid, which maintains the integrity of capillary walls and thus helps to increase capillary integrity and aids in preventing abnormal capillary permeability, fragility and bleeding. They were recommended to correct all ailments involving bleeding, including habitual and threatened abortion; postpartum bleeding; epistaxis, otolaryngology, tonsillectomy; purpura, ecchymosis; hypertension; "little strokes"; diabetic retinitis, ocular disorders; bleeding gums, gingivitis, pyorrhea, periodontal conditions; menorrhagia, RH incompatibility; certain respiratory conditions; rheumatoid arthritis; hermorrhagic duodenal ulcer and ulcerative colitis; hemorrhagic cystitis; postoperative bleeding; and radiation therapy (A. 306–318, 398).

After enactment of the 1962 Amendments, petitioner's products, together with a large number of other bioflavonoid products, were reexamined by the Food and Drug Administration under the drug effectiveness

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[4] Because of the 1962 Amendments, FDA, by regulation adopted May 28, 1968, revoked all opinions previously given that products were not new drugs. 33 Fed. Reg. 7758, 21 C.F.R. 130.39 (A. 291).

criteria contained in the new provisions of the law.[5] The initial review was undertaken by NAS-NRC panels under the drug efficacy study program (described in our brief in *Bentex* at pp. 16–19). In the words of the NAS-NRC Panel on Drugs Used in Metabolic Disorders, "everything from threatened abortions to bleeding gums is reported to have responded" to treatment with citrus bioflavonoids. This Panel's evaluation was that the "use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved." See App. A, *infra*, p. 56. The NAS-NRC Panel on Drugs Used In Hematologic Disorders found, in the words of one of its members, that there was no demonstration "in any form, in any combination, with respect to the bioflavenoids" that these products are efficacious for any medical use (A. 347).

These conclusions were based on a consideration of the material submitted by USV and others marketing bioflavonoid products, on information available in the published medical literature, and upon the informed judgment of the panel. The expert groups considered all the bioflavonoid preparations in terms of their claimed usefulness in bleeding disorders and found no evidence of efficacy for any bioflavonoid, including USV's, for any bleeding state in man (A. 344–345, 359–360). Reports of the panel findings were transmitted to the agency.

On January 23, 1968, the Food and Drug Administration announced that, after considering the NAS-NRC reports concerning bioflavonoid compounds, it

[5] FDA's implementation of the 1962 Amendments is described in the government's *Bentex* brief at pp. 16–23.

had concluded from the reports and its own evaluation that there was no evidence that these drugs are effective for use in man for any condition. 33 Fed. Reg. 818 (A. 290). The notice advised interested persons that the Commissioner of Food and Drugs intended to publish a notice of opportunity for hearing on a proposal to withdraw approvals for all "new-drug applications" for drugs containing these compounds, alone or in combination with other drugs. The announcement was made to notify interested persons and to invite all persons who might be adversely affected to meet and discuss problems arising from the agency's intentions (*ibid.*).

On July 10, 1968, FDA issued a formal notice of opportunity for hearing on its proposal to withdraw approvals of the NDAs on these products, including petitioner's nine products covered by NDAs 9965, 11474 and 11475.[6] 33 Fed. Reg. 9908 (A. 293–296). Petitioner then filed this suit in the district court, seeking a declaratory judgment that its drugs are exempted from compliance with the efficacy requirements of the 1962 Amendments by the provisions of Section 107(c)(4) (A. 275).

In the meantime, the administrative proceedings went forward. USV sought a postponement because of the pending litigation concerning its products' status, but the Commissioner declined to stay the proceedings. Petitioner submitted no evidence of adequate and well-controlled clinical investigations to support

[6] We are here utilizing the phrase "covered by" in the sense that we contend it is used in Section 107(c)(4) of the 1962 Amendments. Two of the nine products were not actually named in any of these NDAs (see p. 6, *supra*).

its claims of effectiveness, and the Commissioner, on October 15, 1970, concluded that there was a lack of substantial evidence that petitioner's products, for which NDAs had been in effect, were therapeutically effective as claimed in their labeling. Approvals for petitioner's NDAs were therefore withdrawn.[7] 35 Fed. Reg. 16332 (A. 297–298).

In the district court, petitioner contended that its products were exempted by Section 107(c)(4) because (1) they had been sold in the United States on the day prior to enactment of the Drug Amendments of 1962 (*i.e.*, October 9, 1962); (2) they were not new drugs under the 1938 Act because they were generally recognized as safe; and (3) they were, in petitioner's view, not "covered by an effective application." In support of its claim of general recognition of safety, petitioner offered the testimony of three physicians, Drs. Karpman (A. 422–434), Clemetson (A. 434–442)

[7] On petition for review, the Court of Appeals for the District of Columbia Circuit reversed the Commissioner's decision, because the Commissioner's notice of opportunity for hearing and final order failed to set forth the facts and reasons relied upon in denying petitioner the hearing it had requested and in withdrawing the NDA approvals. *USV Pharmaceutical Corporation* v. *Secretary of Health, Education and Welfare*, 466 F. 2d 455. Although the government believes the court of appeals was in error insofar as its opinion would impose on the Commissioner a burden of coming forward with evidence of inefficacy before refusing to hold an evidentiary hearing (an alternative ground of decision), it did not seek review of the decision in this Court. The proceedings on remand are now pending before the Commissioner, but action on USV's request for a hearing has been stayed pending a decision in *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394, since the operation of FDA's regulations governing availability of hearings are at issue in that case.

and Miller (A. 442–463). Petitioner also relied on the government's stipulation that its products would not cause toxic adverse reactions in normal individuals. To establish that its products were not "covered by" effective applications, it relied upon the 1961 statement of the Director of FDA's New Drug Branch that "[i]n our opinion" Prednis-CVP and Prednyl were not new drugs, on its assertion that CVP products were no longer considered to be new drugs a short time after the NDA became effective (A. 300–301), and on the statement of its counsel that petitioner had not complied with FDA regulations requiring the submission of information concerning new labeling and changes in the method of manufacture of new drugs (A. 451–452).

On April 1, 1971, the district court held that two of petitioner's products had never been covered by effective NDAs and that the other seven had been covered at one time, but that these applications had later been withdrawn by petitioner. It further found that the products were "safe" for use in treating capillary permeability and fragility.[8] It therefore concluded that, as of the day the 1962 Amendments

[8] The government had relied on the testimony of Dr. Spaet, who had served on the NAS–NRC hematology panel and had the primary responsibility for the evaluation of bioflavonoid drugs, and of Dr. Corn, another expert witness, to show that petitioner's products were not safe because they were not effective to treat any condition involving bleeding, whether resulting from capillary permeability or fragility or any other condition (A. 371–422). However, since the question was not presented in the petition for certiorari, it is not necessary on this record to determine whether, as a matter of law, a product could have been unsafe prior to the Drug Amendments of 1962 because it was ineffective in treating the conditions for which it was recommended in its labeling.

became effective, petitioner's products were not new drugs, were not covered by effective applications within the meaning of Section 107(c)(4), and hence were exempted from the effectiveness criterion added to the regulatory provisions of Sections 505 and 201(p) (A. 463–466). In so ruling, the district court necessarily determined that it, and not the Food and Drug Administration, had jurisdiction to decide exemption questions.

On appeal, the court of appeals, while agreeing that the district court alone had jurisdiction,[9] reversed on the merits and held that none of petitioner's bioflavonoid products were entitled to the Section 107(c)(4) exemption (A. 466–473). As to the seven drugs for which NDAs had been filed, the court stated that USV was without authority to withdraw an NDA once it was effective. Therefore, even if the drugs were generally recognized as safe on October 9, 1962, they nevertheless were "covered by an effective application" within the meaning of Section 107(c)(4) and thus were not exempt from the drug effectiveness requirements of the 1962 Amendments (A. 468–470). As to the two "me-too" drugs,[10] the court held that, although the me-toos of other manufacturers competing with USV's bioflavonoids would be exempt, USV's me-toos were not exempt because the NDAs covering its pioneer drugs, which were personal to USV, covered all of its products similar in

[9] This issue is discussed in the government's brief in the *Bentex* case.

[10] Use of the term "me-too," which describes identical, similar, and related drug products, is explained in the government's brief in the *Bentex* case at p. 7, and at 37 Fed. Reg. 23185, which added Section 130.40 to 21 C.F.R.

formula and labeling (A. 470–473). In response to USV's petition for certiorari, the government agreed that USV's me-too products should be accorded the same treatment as me-toos of other manufacturers who had never filed NDAs for any bioflavonoid product; the government and USV disagree, however, on what that treatment should be.

SUMMARY OF ARGUMENT

This case presents issues of the scope of the exemption afforded to some drugs on the market at the time of adoption of the 1962 Drug Amendments by the provisions of Section 107(c)(4).

The legislative history of the 1962 Amendments shows that the Senate originally reported a bill that, by excluding effectiveness from the definition of "new drug" in Section 201(p), would have made all drugs then on the market exempt from new drug regulation for effectiveness if they were not "new drugs" as of 1962 under the old, safety-only definition. However, that bill was not enacted. Instead, after the thalidomide tragedy came to light, substantial revisions were made to the bill, including the addition of transitional provisions in Sections 107(c)(2) and 107(c)(3) making the drug effectiveness provisions specifically applicable to drugs already on the market, with a limited exception in Section 107(c)(4) for drugs which had "never been subject to" new drug regulation.

The construction of Section 107(c)(4) basically adopted by the court of appeals and urged here by petitioner would exempt from the Amendments' efficacy requirements any individual drug product not

specifically named in an application filed with the agency before 1962, even though one or more pharmacologically identical products that differ only in having been specifically named in an NDA would be subject to removal from the market for failure to establish effectiveness. This discrimination between "me-too" and "pioneer" products, which are identical to one another for any relevant regulatory purpose, is irrational and would raise serious constitutional problems. It would also, because the quantity of me-too products on the market far outnumbers the NDA'd versions of most drugs, create a situation in which, contrary to the apparent congressional purpose and expectation, the coverage provisions of Section 107(c) would be overwhelmed by the exemption provision. Since the legislative history contains no evidence that Congress intended such results, this Court should reject petitioner's construction of Section 107(c)(4).

With respect to its NDA'd products, petitioner contends that the applications in which they were named were no longer "effective" within the meaning of Clause (C) of Section 107(c)(4) because petitioner had "withdrawn" or "inactivated" them. This argument was rejected by the court of appeals, which held that an application that had gone into effect at any time prior to 1962 remained an effective application for purposes of the exemption provision regardless of the manufacturer's subsequent actions with respect thereto. This aspect of the court of appeals' holding is directly supported by the explanation in the Amendments' legislative history that the exemption provision applies to drugs that had "never been subject to" new

drug regulation, a description that obviously does not fit petitioner's NDA'd products. Moreover, petitioner's proposed construction would be subject to the same irrationality objections as its interpretation of the application of Section 107(c)(4) to me-toos, since it would impose arbitrary discriminations among identical products depending on how the manufacturer had treated the NDA after an effective application was no longer required for the marketing of the product.

The arbitrary and debilitating results that would follow from petitioner's interpretation of Section 107(c)(4) are not required by the language or structure of the statute. They hinge upon an unsubstantiated assumption that the word "drug" as used in that provision refers to an individual drug product rather than, in a generic sense, to a class of identical or substantially similar products related to one another by chemical composition and therapeutic use. The logic of the statute, however, indicates that the word "drug" was used generically in Section 107(c)(4). Only under this approach does the statute have a coherent meaning, which both effectuates the legislative purposes underlying its enactment and avoids unwarranted discrimination among identical products on the basis of historical peculiarities of marketing wholly unrelated to the regulatory objectives of the efficacy provisions.

Under this generic approach, the existence of an effective NDA with respect to any member of the generic class means that the drug, generically, is "covered by an effective application," from which it follows, *a fortiori,* that any example of the drug is also "cov-

ered" and ineligible for the exemption by virtue of Clause (C) of Section 107(c)(4). Similarly, the generic approach prevents the operation of the statute from turning on idiosyncracies of an individual product's pre-1962 regulatory history, since the inquiry would always be directed to the characteristics of the drug's generic class.

The generic approach is, moreover, mandated by the structure of the statute. Section 107(c)(4) is by its terms addressed to the application of Section 201(p)'s amended definition of "new drug." Since Section 201(p) clearly deals with drugs generically, its amplification in Section 107(c)(4) should be read in the same sense. The fact that drugs are not dealt with generically under Section 505, which establishes procedures for the content and evaluation of new drug applications, is entirely consistent with a generic approach to Section 107(c)(4). Applications are perforce physical documents submitted by particular persons and describing singular products, and it is manifestly appropriate that the portion of the legislation establishing procedures for dealing with these concrete entities, as well as the administrative practices developed in connection therewith, should assume a personalized and particularized character. But the particularized approach of Section 505 is inappropriate for the broader regulatory objectives of Sections 201(p) and 107(c)(4).

The generic approach to Section 107(c)(4) gives that exemption provision a limited but reasonable meaning that is wholly consonant with the congressional purposes in establishing efficacy requirements

for drugs while allowing a limited exception therefrom. There were a significant number of drugs marketed between 1938 and 1962 (almost entirely in the over-the-counter category) that consisted solely of old, established ingredients that had long been generally recognized as safe, but which, because they consisted of a new combination of ingredients or because they advanced new claims, would not be entitled to "grandfather" status under the 1938 Act. Unless such drugs proposed increased dosages or involved new combinations of components about which some safety question might have arisen, they would "never have been subject to" new drug regulation and would fit precisely within the class identified by Congress in the committee reports and debates as being exempted by Section 107(c)(4) from the effectiveness requirements of the 1962 Amendments. Otherwise, those requirements became applicable to pre-1962 drugs after a two-year grace period under the other provisions of Section 107(c).

ARGUMENT

I

THE STRUCTURE AND LEGISLATIVE HISTORY OF THE 1962 DRUG EFFECTIVENESS AMENDMENTS AND OF THE TRANSITIONAL PROVISIONS OF SECTION 107(C) INDICATE THAT THE EXEMPTION PROVISION OF SECTION 107(C)(4) SHOULD BE NARROWLY CONSTRUED

1. The basic thrust of the 1962 Amendments is to require manufacturers of drugs to establish their effectiveness for claimed uses, as well as their safety, before the products can lawfully be marketed. To accomplish this, Section 201(p) of the Act was amended to

redefine a "new drug" (*i.e.*, a drug subject to premarketing clearance by FDA) as one not generally recognized by experts as both safe and effective for use under the conditions prescribed;[11] Sections 505(a), (c) and (d), which had previously provided that an NDA would automatically become effective unless an order was issued refusing to permit it to become effective, were amended to require affirmative approval by FDA; Section 505(d), which deals with the procedures for administrative action on NDAs, was amended to require disapproval of an application if there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have"; and Section 505(e) was amended to require that any previously granted approval of an application be withdrawn whenever it appears from new information or otherwise that there is a lack of substantial evidence of the drug's effectiveness.

In Section 107(c) of the 1962 Amendments, Congress dealt with the problem of the application of the new drug efficacy provisions to drugs already on the market at the time of enactment of the Amendments. Without this transitional provision, all such drugs—except those marketed prior to the enactment date of the basic Act (June 25, 1938) whose labeling had not been changed, which were exempted from "new drug"

[11] The definition of "new drug" in Section 201(p) also includes a requirement that the drug be used "to a material extent or for a material time" (A. 475). For purposes of conciseness of expression, this brief usually refers to "general recognition" in discussing the criteria for "new drug" status. Such reference should be deemed to include the "use" requirement also imposed by the statute.

status by Section 201(p)—would immediately have been in violation of the amended Act unless generally recognized as effective. Even the approximately 9,000 NDAs which had become effective would not have authorized continued marketing of the products to which they applied, because the applications had not been affirmatively approved by FDA under the new criteria.

Section 107(c) contains four subparagraphs. The first subparagraph defines the term "enactment date" as the date of the enactment of the Amendments (October 10, 1962) and the term "basic Act" as the Federal Food, Drug, and Cosmetic Act.

The second subparagraph, Section 107(c)(2), is addressed to particular new drug applications on individual products filed prior to the Amendments. It provides that applications which were "effective" on the day before the enactment date shall be deemed to be "approved" under the Amendments. This provision was necessary because, under the original Act, NDAs had not been administratively approved; rather, they became automatically effective after a fixed period unless the Secretary refused to permit them to become effective. The amendments to Section 505(a) and (c), however, imposed a requirement of formal approval. Section 104, P.L. 87–781, 76 Stat. 784. Section 107(c)(2) thus eliminated the necessity to review and approve every application already on file.

The third subparagraph, Section 107(c)(3), is also concerned with particular applications previously on file. It provides that the amended provisions for the filing of an NDA in Section 505(b) and for approvals

or refusals to approve under Section 505(d), insofar as they relate to the effectiveness of drugs, shall not apply to applications already in effect, so long as the application is not withdrawn or suspended under Section 505(e), if the labeling remains unchanged. It further provides that in any proceedings to suspend or withdraw such an application, the new effectiveness requirement in the withdrawal provision, Section 505(e), shall not apply until October 10, 1964, or until the application is withdrawn for reasons other than lack of drug effectiveness, whichever comes first. Manufacturers were thus assured that they could continue marketing previously NDA'd products unless and until the NDA was withdrawn, and that before such a withdrawal could occur on the new efficacy grounds, they would be afforded a minimum of two years within which to compile "substantial evidence" in the form of adequate and well-controlled studies (see Section 505(d)) to support the claims for their products.

Finally, in Section 107(c)(4), Congress exempted certain drugs from the new effectiveness requirements, so long as their composition and labeling remained unchanged. In order to benefit from this exemption, a product would have to satisfy three requirements: (A) it must have been commercially used or sold in the United States on October 9, 1962; (B) it must not have been a new drug as defined in the pre-amendment Act (*i.e.*, it must have been generally recognized by experts as safe); and (C) it must not have been "covered by an effective application under section 505 of that Act" (A. 482).

The two issues presented in this case turn upon the proper interpretation of Section 107(c)(4): whether "me-too" copies of an NDA'd drug product are subject to the efficacy requirements to the same extent as the NDA'd product itself depends on the interpretation of the phrase "drug * * * covered by;" whether the NDA'd product may itself be exempted in certain circumstances depends on the interpretation of the word "effective." With respect to the first question, the court of appeals held that only the products named in the NDA (or me-toos of the same manufacturer) are "covered," and therefore identical or similar copies marketed by other manufacturers would be eligible for the exemption; we contend, on the other hand, that the phrase "drug * * * covered by" should be given a broader, generic meaning, so that me-toos would be subject to the same regulation for effectiveness as the NDA'd products they duplicate. With respect to the second question, the court of appeals agreed with the government's view that an NDA that became effective prior to 1962 remained effective for purposes of Section 107(c)(4) regardless of the subsequent history of the product, so that all products NDA'd between 1938 and 1962 are therefore ineligible for the exemption; petitioner urges that an NDA could cease to be effective, and the product therefore exempt, if the manufacturer had taken steps to inactivate or withdraw the NDA.

2. One of the major defects in the 1938 Act upon which Senator Kefauver's investigations of administered prices in the drug industry [12] focused was its

[12] See our brief in *Bentex* at pp. 10–11.

failure to prevent the marketing of drugs as to which there was no scientifically reliable evidence that they would be effective for the uses for which they were promoted. Testifying in 1961 in support of S. 1552, the bill that ultimately was adopted as the 1962 Amendments, then Secretary of Health, Education, and Welfare Ribicoff provided examples of drugs that FDA had been forced to approve for marketing despite the absence of any appropriate medical evidence that the drugs would actually do what was claimed for them (citrus bioflavonoids, the drugs involved in the present case, were among those singled out by Secretary Ribicoff as coming within this category).[13]

On July 19, 1962, the Senate Committee on the Judiciary reported a bill designed to "keep unfit drugs off the market * * * and speed their removal should they reach the market." S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess., p. 8 (hereinafter referred to as "Senate Report"). The Committee recommended amendments to Section 505 of the Food, Drug, and Cosmetic Act, the provision governing the processing of NDAs, under which approval and withdrawal of approval would turn on evidence of efficacy as well as of safety. However, the reported bill did not propose any amendment of the definition of "new drug" in Section 201(p), so that any drug that was generally recognized as safe by qualified experts would not be subject to the Act, and thus not subject to its new efficacy requirements (*id.* at 17). Had the

[13] See Hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary, United States Senate, 87th Cong., 1st Sess., pursuant to S. Res. 52 on S. 1552, Part 5, pp. 2583–2585.

bill been enacted in this form, the result would have been that drugs then on the market would have been exempted from the efficacy requirement unless they were not then generally recognized as safe—in other words, as applied to drugs already on the market, the bill as initially reported would have had the same effect as the bill actually enacted would have if Clause (C) of Section 107(c)(4) were eliminated.

Senator Kefauver dissented from this aspect of the report, contending that if the definition of "new drug" were not amended to include effectiveness, new claims for, or variants of, products previously cleared under Section 505 would not be subject to efficacy review (*id.* at 36–37). The Committee majority rejected this view, pointing out (correctly) that such new uses already required clearance for safety under the 1938 Act, and therefore they would require clearance for effectiveness under the proposed amendments (*id.* at 17; see also statement of Senators Dirksen and Hruska, *id.* at 60–61). Had the bill been enacted in this form, petitioner's contention (Br. 52–60) that Congress did not seek to apply the efficacy provisions to safe drugs then on the market would have considerable force. But it was not.

Instead, at about the time the Committee reported out the initial version of the bill, the Nation (and the Congress) was jolted by news of the thalidomide tragedy. On August 3, 1962, President Kennedy submitted to the chairman of the Senate committee drafts of further amendments for the Committee's consideration which, the President stated in his letter of transmittal, "* * * will help assure the American people

that any drug on the market today is safe and effective for its intended use * * *." *Public Papers of President John F. Kennedy* 603 (1962). The committee thereupon met in executive session on six occasions between August 6 and August 20, and, on August 21, reported out a bill amended in a number of respects from the July version. Senate Report, Part 2, p. 1.

One of the amendments added general recognition of effectiveness to the "new drug" definition in Section 201(p). This change was stated to be for the purpose of eliminating "any possible ambiguity" regarding the problem that had disturbed Senator Kefauver (*id.* at 5). Petitioner contends that this limited expression of purpose shows that Congress did not intend by this change to subject drugs already on the market to the new effectiveness criteria (Br. 55). There is no reason, however, to resolve that contention in isolation, since Congress made clear its general intention that the new requirements would apply to such drugs by its adoption of the transitional provisions in Section 107(c). Subparagraphs 2 and 3 of that Section (as explained at pp. 19–20, *supra*) established the basic proposition that drugs then on the market with effective NDAs would be considered to have approved NDAs and could continue to be marketed but would, after a two-year grace period, be subject to removal from the market through NDA withdrawal proceedings on inefficacy grounds. Section 107(c)(4) created an exception from this general policy only for drugs then on the market that were generally recognized by experts as safe *and* were not "covered by an effective application."

That this exception from the general principle was intended to be a limited one was made clear by the report (Senate Report, Part 2, p. 8; emphasis supplied):

> Thirdly, in the case of a drug on the market which was *never subject to the new-drug procedure before,* the amendments to the new-drug definition relating to drug effectiveness would not apply to existing labeling claims.

Senator Eastland explained the transitional provisions in a similar manner on the Senate floor (108 Cong. Rec. 17366; emphasis supplied):

> As a result of the change in the definition of "new drug" and the addition of the new effectiveness test, it is necessary to include transitional provisions. Under these provisions, the new effectiveness test, in the case of drugs previously cleared under a new drug application, will apply only to new or amended claims *unless [approval of] the application is withdrawn or suspended.* Withdrawal on the ground of a lack of substantial evidence of effectiveness will not apply, for a period of 2 years, to existing claims, unless the approval of any of the claims is withdrawn on other grounds. Established drugs *which have never been required to go through new drug procedures* will not be affected by the new effectiveness test insofar as their existing claims are concerned.

Petitioner's argument that the post-thalidomide revisions to the legislation had "a clear, narrow and limited [purpose]—to insure that 'an NDA'd drug would not make new, unsupported claims of efficacy' " (Br. 59–60) is thus erroneous. The bill would have

achieved this purpose under both the original and the amended version, and, as Senator Eastland made unmistakably clear, the added "transitional provisions"—and it is significant that he used that term—had the further effect of permitting FDA to withdraw or suspend an NDA for inefficacy with respect to *existing* claims after the two-year grace period.

Substantially the same explanation appears in the House Report (H. Rep. No. 2464, 87th Cong., 2d Sess., pp. 8, 12) and the Conference Report (H. Rep. No. 2526, 87th Cong., 2d Sess., pp. 22–23) both of which similarly refer to Section 107(c) as adding "transitional provisions." The history of the amendments in the House sheds little new light on the congressional intent and affords no concrete support for petitioner's contention (Br. 58–59) that Section 107(c)(4) was a compromise designed to exempt me-toos from efficacy regulation. If anything, it tends to confirm that the basic thrust of the legislation was to cover pre-1962 drugs, with a limited exemption carved out for drugs that, as a generic class, had always been recognized as safe from the time they first went on the market.[14] (See discussion at pp. 42–52, *infra*.)

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[14] In May 1962, Representative Harris, Chairman of the House Committee on Interstate and Foreign Commerce, introduced H.R. 11582, 87th Cong., 2d Sess., to give effect to a part of President Kennedy's message on consumer protection. This bill provided for the inclusion of efficacy in the definition of "new drug" and in the administrative provisions in Section 505. It also contained, in Section 108(c), transitional provisions similar in effect to Section 107(c)(3) of the final Act, which would have had the effect of subjecting all pre-1962 drugs to the efficacy requirements. Hearings were held on the House bill before and after the Senate had passed S. 1552 in August 1962. *Drug Industry Act of 1962*, Hearings before the House Com-

In summary, beyond repeated statements to the effect that Section 107(c)(4)'s exemption applies to drugs that were "never subject" to new-drug regulation and was part of "transitional provisions" for applying the efficacy requirements to "existing" drug claims, Congress provided little elucidation of the scope and application of the exemption. However, there are indications that the distinction that Congress had in mind was between "ethical" or prescription drugs, and so-called "proprietary" or "over-the-counter" drugs. Prescription drugs, which by definition involve products that may be dangerous unless

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mittee on Interstate and Foreign Commerce, 87th Cong., 2d Sess. on H.R. 11581 and 11582 (June, August 1962). At these hearings, one witness for the Pharmaceutical Manufacturers Association urged the position initially adopted (but subsequently rejected) by the Senate Committee, *i.e.*, that old drugs already on the market should not be subject to the effectiveness requirement, and that the NDA for new drugs cleared before the amendment should be withdrawn or suspended only if the product were unsafe. *Id.* at 238. The witness for the Proprietary Association, noting that most proprietary medicines had not been subject to new drug procedures, suggested that the revised definition of new drug should not apply to any drug intended for use under conditions set forth in its labeling on the date the amendments were enacted. *Id.* at 369. Responding to these suggestions, the FDA asked why ineffective drugs should be promoted because the manufacturer started selling "before a serious flaw in the act was corrected? On the other hand, we do not propose that these thousands of drugs be summarily taken off the drugstore shelves. We, of course, would suggest a reasonable transition provision." *Id.* at 573. As reported, the House bill included in Section 107 the provisions originally proposed, plus a new paragraph (d) closely parallel to present Section 107(c)(4). Nothing in this history suggests an intent to create an exemption that, in operation, would exclude the vast majority of pre-1962 drug products from the efficacy requirements.

administered under medical supervision,[15] would not be exempted because they almost invariably had been subject to the new drug regulatory procedures. Proprietary drugs, which were considered safe enough to be self-administered, consisted in many instances of relatively innocuous substances and therefore may never have been subject to "new drug" regulation. This is borne out by the testimony of a representative of the Proprietary ~~Drug~~ Association in the House hearings, see n. 14, *supra*. It is also supported by Senator Kefauver's explanation during the debates of differences in the bill's application to these two classes of drugs (108 Cong. Rec. 17368):

> Effectiveness, as well as safety, should apply to new proprietary drugs, but proprietaries now on the market are not to be subject under the present bill to the provisions requiring them, upon notice by the FOA [sic], to support their claims for effectiveness. I think they should be so required. That is a matter which can be remedied in conference or by other legislation.[16]

Even more significant than what the legislative history affirmatively reveals about congressional intentions, for purposes of the statutory interpretation

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[15] Under Section 503(b) of the Act, 21 U.S.C. 353(b), prescription drugs are products which may be habit forming, which for safety reasons should be administered only under supervision of a physician, or which are designated in the NDA as requiring distribution only by prescription. Such drugs, if marketed without prescription, are deemed misbranded.

[16] While this statement is generally accurate, there were in fact several hundred NDAs that became effective prior to 1962 for "proprietary" products. Those products, and their me-too copies, would of course be subject to the same regulation under Section 107(c) as similarly situated prescription drugs.

issues presented in the instant case, is what is absent. Petitioner has failed to cite, and we have been unable to find, a single reference indicating that Congress was aware of the regulatory status of me-too drug products—that for every product named in an NDA there were numerous identical or similar products on the market for which no NDA had ever been filed—and considered this situation in formulating the transitional provisions. On the contrary, it is apparent that when the word "drug" was used in the reports and debates, with respect to Section 107(c)(4), it was used in the generic sense to refer to a chemical compound or class of compounds rather than to refer to a particular brand or product.

II

THE EXEMPTION IN SECTION 107(c)(4) SHOULD BE CONSTRUED TO EXCLUDE FROM THE AMENDMENTS' EFFICACY REQUIREMENTS ONLY THOSE DRUGS WHICH, AS A GENERIC CLASS, WERE NEVER SUBJECT TO NEW DRUG REGULATION PRIOR TO 1962

Petitioner contends that it is exempted by Section 107(c)(4) from being required to establish the effectiveness of nine citrus bioflavonoid products that it has been marketing since before 1962. Seven of these products were named in three NDAs that became effective prior to 1962, while the other two were "me-toos" that were never the subject of an NDA. The two categories of products present different, although related, issues, the resolution of which depends upon the interpretation of three phrases in the provision, each of which is here italicized:

> In the case of *any drug* which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not *covered by* an *effective application* under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day. [Section 107(c)(4); emphasis added.]

The interpretation of the phrase "any drug" is important to the resolution of both issues presented by this case. It is our view that the phrase should be read in a generic sense, *i.e.*, as referring to pharmacologically identical or substantially similar classes of items defined by chemical composition and therapeutic use.[17] Under this interpretation, all drug products belonging to the same generic grouping would be treated the same for purposes of Section 107(c)(4) regardless of the particular history of any individual product. Petitioner, on the other hand, urges an approach under which the phrase would refer to individual drug products and the application of the provision to each individual product would turn on its peculiar regulatory history.

The interpretation of the phrase "covered by" is involved in the resolution of the me-too issue. Under petitioner's view, a particular drug product is "covered by" an application only if it was itself the subject of the application. Under the government's in-

[17] As used in this brief, "generic" always has this meaning.

terpretation, such a product is "covered by" an application if it is a member of a generic class, any one of which had been the subject of an NDA.

Finally, the interpretation of the phrase "effective application" is critical to the issue of FDA's power to withdraw approval of petitioner's NDAs for failure to establish efficacy. In the government's view, concurred in by the court of appeals, an application once filed remains "effective" for purposes of this provision regardless of the manufacturer's subsequent actions or of subsequent general recognition of the drug's safety. Petitioner urges that actions taken by the manufacturer to withdraw or inactivate the application would cause it to cease to be "effective" within the meaning of the provision.

A. PETITIONER'S INTERPRETATION OF SECTION 107(C)(4) AS APPLIED TO ME-TOO DRUG PRODUCTS WOULD DEFEAT THE BASIC PURPOSE OF THE STATUTE AND WOULD CAUSE ARBITRARY AND UNWARRANTED DISCRIMINATION AMONG MANUFACTURERS OF IDENTICAL PRODUCTS

Are me-too drug products "covered by" applications filed with FDA on identical drug products (either by other manufacturers or for other brands of the same manufacturer [18])? The phrase "covered by" is not defined in the Act and has no obvious inherent meaning. As a matter of pure language, considered

[18] The court of appeals distinguished between these two situations, holding that me-toos would be exempt from efficacy regulation in the former situation but not the latter. We agree with petitioner that the distinction is unwarranted. Our position is that all generically related drug products should be treated the same; but even if they are not, at least all me-toos should be accorded the same treatment.

in isolation, the government's interpretation and petitioner's are equally plausible. As a matter of implementing the statutory objectives and the apparent congressional intent, however, it would make no sense for Section 107(c)(4) to be applied in the manner petitioner suggests.

Petitioner's approach, which turns on the vagaries of the marketing and regulatory history of each individual product, introduces a fortuitous and wholly irrational element into the statutory scheme. Manufacturers who submitted to the congressionally established regulatory procedures and obtained an effective NDA for their products (sometimes hereinafter referred to as "pioneers") would be required to show effectiveness in order to continue marketing them. But their competitors, who produce the same drug for the same uses, would be exempt so long as they never obtained an effective NDA, even if their initial marketing had been illegal or had been made possible only because of the pioneer's NDA. In short, the producer of a drug who obtained the primary NDA would have to show effectivness, while the me-too manufacturer who copied it would not.

The basic purpose of the 1962 Amendments, insofar as here relevant, was to assure the American public that the drugs they use are effective as well as safe.[19]

[19] As Congressman Ryan put it (108 Cong. Rec. 21069):

"Once a company is registered and deemed qualified to produce drugs, the Food and Drug Administration must be given substantial evidence that each drug produced is effective as well as safe. Under present law a company could stick a name on bottled water and attempt to sell it for medicinal use simply because it is not harmful. This has been one of the greatest defects in our existing law; a producer should be required to

As we have indicated in our brief in *Bentex* (pp. 7–8), for every drug product for which an NDA was filed prior to 1962 there were generally a large number of me-too copies that went on the market without their own NDA (current experience indicates a ratio of about 13 to 1). If the interpretation of petitioner and the court of appeals is correct, Section 107(c)(4) would exempt all the me-toos from the efficacy requirements, leaving the Amendments effective only against the pioneers (in addition to post-1962 products). The exemption in Section 107(c)(4) would thus be broadened to the point of almost completely swallowing up the basic legislative action in

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show that his product will do what is claimed of it. When a person pays his money at the drug counter, he should have some degree of assurance of the efficacy of the product he buys."

Congressman Reuss echoed the same thought in explaining the purposes of the proposed drug effectiveness provisions (*id.* at 21070):

"So, as the thalidomide tragedy has shown, the Food and Drug Administration does now have limited authority that can prevent a major disaster resulting from the wide use of an unproven, insidious drug. But, the limited authority FDA now has is not enough to assure the high standards of quality, the reliability, and the effectiveness that our citizens have a right to expect in the drugs they take.

"All of the provisions in H.R. 11581 are important and necessary for the public good, but if I should point to one as being most important, it would be the provision that new drugs be proved effective before they are marketed.

"A dismal proportion of consumers' resources are spent on worthless drug products. This unnecessary and wasteful extravagance might not be so bad if it were not coupled with the deplorable fact that ineffective drugs can mean the difference between a man's health and sickness or his life and death. The bill before us would help to assure our sick that the drugs they take will in fact be effective in their purpose."

Sections 107(c)(2) and 107(c)(3) authorizing FDA to withdraw marketing appoval for pre-1962 drugs of unproved effectiveness, leaving those provisions an empty and meaningless shell (whose only effect, in most instances, would be to restrict competition in the marketing of ineffective pre-1962 drugs [20]).

Such a self-defeating purpose should not be assigned to Congess. Nor should Congress be presumed to have acted with the irrationality inherent in petitioner's construction of Section 107(c)(4). What conceivable purpose could Congress have had in exposing the NDA'd product to removal from the market for failure to establish efficacy while exempting its non-NDA'd twin? Surely if Congress wished to protect the public health and purse by removing the pioneer, it could hardly have intended to insulate the equally ineffective me-too. Conversely, if Congress wanted to protect the me-too from removal even though ineffective, in order to avoid adverse economic impact on the manufacturer as a result of the new requirement (the legislative history, discussed at pp. 21–29, *supra,* shows that it did not), there is no reason why it would have wished to deny the same benefit to the pioneer. A rational basis might be supposed for a discrimination in favor of the manufacturer who had shouldered the burden of submitting to the regulatory procedures under the Act, but none can be supplied for a discrimination against him.

Indeed, the arbitrary discrimination that would be imposed on some manufacturers to the benefit of

[20] The legislative history indicates that Congress was concerned with fostering rather than restricting competition. Senate Report, Part 1, p. 18.

competitors marketing identical products under petitioner's construction of Section 107(c)(4), apart from entailing manifest deviation from congressional intent, would appear to raise serious constitutional problems. See, *e.g.*, *Morey* v. *Doud*, 354 U.S. 457; *Hartford Co.* v. *Harrison*, 301 U.S. 459; *Mayflower Farms* v. *Ten Eyck*, 297 U.S. 266. See also *Graham* v. *John Deere Co.*, 383 U.S. 1, 5 (pointing out that the Constitution's patent clause imposes limitations on the power of Congress to grant monopolies). In these circumstances, it is a "cardinal principle" of statutory construction that this Court should adopt a construction of the statute by which constitutional problems will be avoided. *Crowell* v. *Benson*, 285 U.S. 22, 62.

The anomalies inherent in petitioner's construction are not vitiated, we submit, by what petitioner characterizes as the "bifurcated nature of the regulatory scheme" (Br. 63–65). It is true that the agency has power to initiate judicial action against ineffective drug products, new or old, under the misbranding provisions of the Act. This remedy is, however, almost completely ineffectual in dealing with the problems created by ineffective pre-1962 me-toos. Since there were, in FDA's estimation, tens of thousands of me-too prescription drug products on the market on October 9, 1962, for which NDAs were not in effect, all of which would remain on the market pending case-by-case removal for misbranding, decades of case-by-case litigation would be required before the congressional goal of removing drugs of unproven effectiveness

from the market could be achieved.[21] As a practical matter, therefore, the theoretical availability of other remedies against ineffective me-toos does not eliminate the unjustifiable discrimination against the pioneer inherent in petitioner's construction.[22]

Moreover, remitting the agency to case-by-case judicial proceedings as the sole remedy for removal of ineffective me-toos from the market would be contrary to the basic scheme of the Act, which, as we have shown in our brief in *Bentex* (pp. 40–47), contemplates that administrative control through pre-

[21] Litigation of a small number of misbranding cases against over-the-counter drug products, with each case taking months or even years to resolve, has consumed an enormous amount of the agency's medical, compliance, and legal personnel resources without making a perceptible dent in the marketing of ineffective over-the-counter drugs. A classic illustration is the agency's attempt over more than a decade to remove from the market phenylpropanolamine drugs promoted for weight reduction. After a number of successful court actions against specific examples of the drug (*e.g.*, *United States* v. *60 28-Capsule Bottles, More Or Less, Etc.*, 211 F. Supp. 207, 214 (D. N.J.), affirmed *per curiam*, 325 F. 2d 513 (C.A. 3), these drugs are still on the market. Hearings on Advertising of Proprietary Medicines before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., pp. 1239–1241. The agency has accordingly abandoned the case-by-case approach to over-the-counter drugs in favor of a broad rulemaking approach. See 37 Fed. Reg. 85, 9464.

[22] This is further emphasized by the difference in burden of proof on the issue of effectiveness in administrative proceedings implementing the Amendments and in judicial proceedings enforcing misbranding provisions—in the former, the manufacturer bears the burden of presenting substantial evidence of the product's effectiveness; in the latter, ineffectiveness must be proved by the government. See *Ubiotica Corp.* v. *Food and Drug Administration*, 427 F.2d 376, 378 (C.A. 6); *United States* v. *60 28-Capsule Bottles, More or Less, Etc*, *supra*.

marketing clearance and subsequent supervision by the expert administrative agency will be the primary safeguard of the public interest. One of the basic purposes of the 1938 Act was to remedy the inadequacies of the Food and Drug Act of 1906, which provided only judicial sanctions against misbranded or adulterated products. The 1962 Amendments were intended to strengthen the system of administrative clearance established under the 1938 Act by extending it to drug effectiveness claims. Indeed, the House Committee Report on the amended bill specifically indicates that it was designed to remedy the inadequacy of restricting the agency's powers with respect to ineffectiveness to case-by-case litigation for misbranding, as a result of which "good medical practice is hampered, and the consumer is misled until, perhaps years later, the Government has gathered the necessary evidence to sustain its burden of proving the violation in court." [23] Petitioner's contention would make this elaborate legislative effort an empty gesture by excluding power to proceed administratively with respect to the thousands of me-too products, thereby rendering virtually pointless the limited regulatory authority petitioner would concede to the agency with respect to NDA'd products.

This Court has often held that statutes should not be so construed that they produce unfair results inconsistent with their spirit and purpose. Rather, where a statute is drafted in a way which is susceptible of more than one interpretation, the courts should select the construction that will best achieve

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[23] H. Rep. No. 2464, *supra*, at 3.

the legislative objective.[24] This principle is particularly important with respect to claims for exemption from statutes intended to protect the public health. *United States* v. *Bacto-Unidisk*, 394 U.S. 784, 798; *United States* v. *Sullivan*, 332 U.S. 689; *United States* v. *Dotterweich*, 320 U.S. 277, 283–284. If Section 107(c)(4) is read, as we contend it should be, to apply to drugs as generic classes, rather than as individual products, it harmonizes with the legislative purpose declared for it, becomes internally consistent, and dovetails neatly into the definition of new drug in Section 201(p), which it modifies.

B. PETITIONER'S INTERPRETATION OF SECTION 107(C)(4) AS APPLIED TO NDA'D PRODUCTS IS ALSO UNREASONABLE AND CONTRARY TO THE EXPRESSED CONGRESSIONAL INTENT

The instant case and the cross-petition in *Hynson* (No. 72–414) both raise issues involving the eligibility for Section 107(c)(4)'s exemption of products that were the subject of an NDA filed between 1938 and 1962, but had, by October 9, 1962, come to be generally recognized as safe.[25] Hynson contends that general rec-

[24] See, *e.g.*, *United States* v. *American Trucking Assn's.*, 310 U.S. 534, 542–545; *Boys Market* v. *Clerks Union*, 398 U.S. 235, 250; *Puerto Rico* v. *Shell Co.*, 302 U.S. 253, 258.

[25] The fact that a drug is not toxic does not necessarily establish that it was generally recognized as safe by qualified experts within the meaning of Section 201(p) of the 1938 Act. Safety is a relative concept. Some drugs which are highly dangerous may be generally accepted as safe for use in treating extremely serious or life-threatening conditions, because the condition itself is more hazardous to the patient than the dangers of the drug. Conversely, ineffective but non-toxic drugs may be considered unsafe for use in treatment of serious conditions, if their

ognition of safety by that date, by removing the product from new drug status and regulation, is sufficient to meet the requirements for exemption from efficacy regulation. We answer that contention in our brief in No. 72–414.

Petitioner in the instant case concedes *arguendo* that mere termination of "new drug" status in that sense was not sufficient to satisfy the requirements of Section 107(c)(4). It contends, however, that in this case other steps were taken by the manufacturer and acquiesced in by FDA that had the effect of withdrawing the NDAs prior to October 9, 1962. In such circumstances, petitioner argues, the NDA should not be considered "effective" for purposes of Clause (C) of Section 107(c)(4). The court of appeals held, however, that petitioner had no power to "withdraw" the applications, and that petitioner's NDA'd products were therefore "covered by an effective application" and ineligible for the exemption from efficiency regulation. We agree.

The simplest answer to petitioner's contention is that it is directly contrary to the congressional explanation of the effect of Section 107(c)(4), reiterated in the Senate report (Part 2, p. 8), the House report (H. Rep. No. 2464, *supra,* at 12), the Conference report (H. Rep. 2526, *supra,* at 22–23), and Senator Eastland's explanation of the bill (108 Cong. Rec. 17366). Each of these sources specifically explains that the provision would exempt drugs that had *never* been

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use displaces effective therapy and thereby jeopardizes the patient's health or life (A. 334–335). The expert judgment involved turns on a balancing of risks.

subject to new drug regulation. See pp. 25–26, *supra*. No other category of drugs was said to be qualified for the exemption. Whatever steps petitioner may have taken to withdraw or inactivate its NDAs,[26] and whatever arguments it may advance on behalf of its me-too products, it obviously cannot, with respect to its NDA'd products, satisfy the congressionally intended requirement that in order to enjoy exempt status a drug must "never" have been subject to new drug regulation.

Even had Congress not clearly stated its intention that a drug that was subject to new drug regulation

[26] We do not agree that petitioner "effectively withdrew" its applications on bioflavonoid products. Its carefully phrased correspondence with the agency prior to the Amendments (A. 299–301) did not state that any application was being withdrawn. Rather, it simply stated that "[i]t is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective" (A. 301). FDA's failure to challenge either petitioner's assertion or petitioner's failure to comply with reporting requirements for new drugs did not mean that the applications were withdrawn for purposes of Section 107(c)(4). The mere failure of an agency with limited resources to prosecute a violation does not, except for the statute of limitations, exempt the violator from the law's requirements. Moreover, as the court of appeals rightly observed, nothing in the 1938 Act authorizes a manufacturer to withdraw an NDA, either directly or indirectly, once it has become effective. Indeed, prior to the 1962 Amendments FDA itself had no authority to withdraw an NDA; it could only suspend the effectiveness of an application under specific substantive and procedural standards. See Section 505(e), 52 Stat. 1053. In view of the specificity with which Congress delimited the powers of the agency and the absence, prior to 1962, of any reason for the FDA to enforce reporting requirements against noncomplying holders of inactive NDAs, petitioner's purported withdrawal had no effect on its products' status under Section 107(c)(4).

at any time prior to 1962 would be subject to the Amendments' efficacy requirements, petitioner's proposed construction would be contrary to the principle that statutory provisions should be construed in a rational manner. Congress could rationally have decided that all drugs on the market in 1962 and generally recognized as safe at that time would be exempted from efficacy regulation simply by showing that they were so marketed and recognized—that is, indeed, what S. 1552 as originally reported in July 1962 would have done (see pp. 22–23, *supra*). But having rejected that approach, Congress had no basis in either policy or fairness to differentiate between products merely according to whether their manufacturer had taken steps to withdraw or inactivate the NDA.

To illustrate, there were 43 applications on file with FDA covering bioflavonoids and related compounds (A. 294–296). Most or all of these were in the same posture in 1962 as regards general recognition of safety, and all are considered of equally unproven effectiveness for their claimed uses by FDA. While the state of activity, inactivity, or withdrawal of these applications varied from one to the next, this provides no rational basis for discriminating among them for the purposes of the Amendment's efficacy requirements. Thus, petitioner's interpretation of this aspect of Section 107(c)(4) is subject to the same irrationality objection as its concept of me-too coverage.[27]

[27] Moreover, if the government's generic interpretation of the provision is accepted with regard to the me-too issue, the alleged "withdrawal" of petitioner's NDAs would be without

Under the generic interpretation, this irrationality is eliminated, since all products in a class of identical or substantially similar drugs are treated in the same manner. If the drug itself was subject to "new drug" regulation for safety prior to 1962, all examples of it are now subject to "new drug" regulation for effectiveness. If it was never subject to safety regulation, generically, none are, in the absence of changed composition or labeling.

C. A GENERIC APPROACH TO SECTION 107(C)(4) FULLY ACCORDS WITH THE STRUCTURE AND PURPOSES OF THE ACT

It is our contention that the word "drug" in Section 107(c)(4) must be accorded a generic meaning if the provision is to have a rational construction consonant with the overall language, structure, and purposes of the statute. Such an approach simply and sensibly resolves all the problems of interpretation presented by the provision. It does so by directing attention to the conformity of the generic drug with the three requirements set forth in the provision and assuring that all members of the class, which are, after all, the same for practical regulatory purposes, are accorded the same treatment. We further submit, contrary to the arguments of petitioner and the conclusion of the court of appeals, that such an approach is entirely consonant with the administrative history of the Act and the recognized personal character of an NDA under Section 505, and that it ascribes a sensible meaning to the exemption provision which conforms to the apparent congressional intent.

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significance, since its products would still be "covered by" the other NDAs on file for similar products, most of which had not been "withdrawn."

1. Section 107(c)(4) modifies the application of Section 201(p), the revised definition of "new drug." Section 201(p) deals with drugs generically, not as individual products, and Section 107(c)(4) accordingly should be given the same generic meaning. Section 201(p) is not concerned with the rights of applicants, details of manufacture or other personal factors, as is Section 505, but with "[a]ny drug * * * the composition of which is such that such drug is not generally recognized, among experts * * * as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" (A. 475). Because of its generic character, Section 201(p) permits manufacturers to market their own version of a drug which, generically, is not a new drug under this definition, without submitting to administrative preclearance by FDA, so long as the product's composition and labeling do not depart from the recognized generic categories.[28] On the other hand, if the product significantly departs from the accepted formulation, use, or method of administration, it becomes a "new drug" because it has deviated from the recognized generic standards.

Obviously, if the word "drug" in Section 201(p) were given an individual product, as opposed to generic, meaning, every new version or brand of every drug would be a "new drug" under the statute, since a particular brand would be unable to achieve the required general recognition and use until it had been marketed for some time. Thus, a non-generic inter-

[28] This has been FDA's interpretation since 1938. See 3 Fed. Reg. 3161, now codified at 21 C.F.R. 130.1(h) and (k).

pretation of the "new drug" definition would lead to the result that no drug product could be put on the market without going through administrative clearance proceedings. No one has ever supposed that the Act has this consequence. Since Section 107(c)(4) is addressed to the manner in which "the amendments to section 201(p) made by this Act" apply to "drugs," the word "drugs" should be given the same interpretation in both Sections.

2. A comparison of the language of Clause (C) of Section 107(c)(4) with that of related provisions of the Act supports the generic approach. In Clause (C), instead of describing exempted products in language turning on whether an NDA for any particular item was in effect, Congress used the broader formula "any drug * * * *not covered by* an effective application * * *" (emphasis added). This "covered by" language appears nowhere else in the Act, either in the original new drug provisions or in the Amendments. It contrasts with the more particularized language of Section 505(a), which was before Congress when the 1962 Amendments were under consideration and which clearly indicates that a new drug application thereunder is personal to the applicant and limited to the particular product upon which it is obtained. Specifically, former Section 505(a) prohibited any person from introducing any new drug into commerce "unless an application * * * * is effective with respect to such drug." And as petitioner recognizes (Br. 27–38), the other provisions of Section 505, and its consistent interpretation by the agency, establish that NDAs under that Section are personal to the manufacturer and particular to his product. If,

in Section 107(c)(4), Congress intended the application of Clause (C) to depend upon the particular status of individual products, it would presumably have used language like that in Section 505, rather than the "covered by" language it chose.

Moreover, this language in Clause (C) similarly differs from that used in the immediately preceding paragraph in the transitional provisions of the 1962 Amendments, Section 107(c)(3). The latter provision (which deals with the status of applications and expressly modifies Section 505) is plainly intended to apply to individual drug products, for it opens with the phrase "In the case of any drug *with respect to which* an application * * * is deemed to be * * * approved * * *." Congress' contrasting use of the phrase "covered by" in Clause (C) of Section 107(c)(4) therefore suggests that it intended to reach more than particular drug products with respect to which an application was in effect. The generic approach we suggest is consistent with that intent.

3. Our interpretation of the language Congress used in Section 107(c)(4) also comports with the regulatory scheme with which Congress was dealing when it enacted the 1962 Amendments. Me-too examples of a generic drug were in fact "covered by" the NDAs of the pioneers in a very real sense. In the ordinary case, particularly in the field of prescription drugs, an application was filed with FDA when a new compound was proposed for use in the treatment of a particular ailment or condition. If this "pioneer" NDA was allowed to become effective, the applicant was then free to market the product. Typically, several other manu-

facturers might file applications for their own examples of this generic drug. After the drug was on the market for a time, it would acquire the necessary general recognition and use to enable it to escape from the "new drug" category. Thereafter, anyone could market a me-too copy free of administrative premarketing regulation, provided his product conformed to the generically accepted formulation and labeling. Had the pioneers not obtained effective NDAs, the drug would not have acquired the necessary general recognition of safety and the required use experience for "not new drug" status, and the me-too products could not have been marketed lawfully without NDAs of their own.

Since the unregulated marketing of the me-too products in 1962 thus hinged on NDAs previously obtained by one or more other examples of the generic drug, the me-toos were, realistically, "covered by" the pioneer NDAs.[29] Thus, when the subject matter with which Congress was dealing in the 1962 Amendments is realistically considered, it is apparent that the words "covered by" were used in Section 107(c)(4) in a

[29] It is immaterial that there were instances in which a "me-too" product was actually marketed prior to the time an NDA became effective for any member of its generic class. Unless the product consisted entirely of substances known to be wholly innocuous and already in wide use for some purposes—which would be very unlikely in the case of a prescription drug (see Section 503(b) of the Act, 21 U.S.C. 353(b))—it was almost certainly a "new drug" under the 1938 Act, and its marketing was illegal without an effective application. If other members of its generic class subsequently obtained NDAs, and if by 1962 the generic drug was not "new" any longer, the me-too product was at the time the 1962 Amendments became effective "covered by" its brothers' NDAs.

sense broad enough to encompass all members of the generic class—regardless of whether the words "any drug" in that Section are also accorded a generic meaning.

4. The analysis adopted by both petitioner and the court of appeals depends almost entirely upon the fact that Section 505 addresses itself to drugs as individual products. We agree that an application under Section 505 is and always has been personal to the manufacturer who files it and particular to the product or products it names. But this is irrelevant for purposes of interpreting Section 107(c)(4), which modifies not Section 505 but Section 201(p), which is concerned with drugs in the generic sense.

Thus petitioner's contention that a generic approach to the interpretation of Section 107(c)(4) represents an about-face from prior agency interpretation is based on an erroneous premise which confuses the personal and individual requirements of Section 505 with the quite different purposes of Section 107(c)(4). In applying the latter provision, it is entirely irrelevant whether, as to any particular product belonging to a generic class for which an effective application was required, the agency may have issued a "not new drug" letter [30] or the manufacturer may have ceased complying with requirements under Section 505. Once the generic class of drugs had become generally recognized as safe, it would have been a pointless waste of the agency's limited resources to continue processing NDAs for new examples of the drug; similarly, if a

[30] Cf. *United States* v. *354 Bulk Cartons * * * Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847, 853–854 (D.N.J.).

manufacturer with an effective NDA had ceased complying with filing, production, and reporting requirements under Section 505 and its implemening regulations, this was of no concern to the agency under the Act as it stood prior to 1962, since the product no longer required an active NDA.[31]

NDAs have been treated as personal under Section 505 in order to insure that administrative regulation of the composition, labeling, and manufacturing of drugs is maintained until such time as the drug attains general recognition of safety (and now effectiveness) and a sufficient history of actual use. It would be ironic indeed if this objective of maintaining administrative control over drugs, embodied in Section 505, were now to be turned by judicial interpretation into the instrument whereby FDA is denied the power to deal effectively with its congressionally assigned task

[31] From an administrative standpoint, however, the application could still be significant, for a product which had ceased to be a "new drug" could again become one in the light of new scientific knowledge. See *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6). Drugs long and widely recognized by qualified experts as safe might subsequently prove to be dangerous in ways not perceived until after many years of use. Recent examples of this phenomenon include cyclamates to reduce sugar intake, see *Eisenstadt* v. *Finch*, CCH Food, Drug, and Cosmetic L. Rep. ¶ 40,392 (E.D.N.Y.), and hexachlorophene in antiseptic washing agents. In the case of hexachlorophene, the drug was originally subject to an effective NDA, and, after it became generelly recognized as safe, the NDAs became inactive and FDA issued "old drug" opinion letters. In light of recent data, the NDAs were reactivated. 37 Fed. Reg. 219, 20160. The reactivated NDA is important since, even though the product has lost its general recognition of safety, it may continue to be a useful drug when marketed under properly limited labeling subject to control by the new drug regulatory procedures of Section 505.

of removing pre-1962 drugs of unproven effectiveness from the Nation's drug counters.[32]

5. Petitioner errs in suggesting that the government's interpretation of Section 107(c)(4) would add nothing to what was already provided in the 1938 "grandfather" provision (Br. 60–63). (Even if petitioner were correct, such a result would be preferable to the arbitrary and discriminatory consequences flowing from petitioner's interpretation, under which the exemption in Section 107(c)(4) would be so broad as to consume almost entirely the provision for regulation enacted in Section 107(c)(3).)

Under the generic interpretation, the exemption is not available to any examples of a generic drug if

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[32] Petitioner attaches undue significance to the fact that Section 505(h) provides for judicial review of an NDA withdrawal only at the behest of the "applicant," contending that if Congress had intended to permit me-toos to be affected by withdrawal of the pioneer's NDA, it would have granted the me-too manufacturer the same avenue of judicial review (Br. 29). In order to ascribe weight to this factor as an indication of deliberate congressional intent, however, it is necessary to assume that Congress was specifically aware of the existence of large numbers of non-NDA'd me-too products and considered the regulatory significance of this fact in shaping the 1962 Amendments. As we have previously stated (see pp. 28–29, *supra*), there is no evidence in the legislative history of such awareness.

Me-too manufacturers are, moreover, subject to no injustice insofar as availability of judicial review is concerned. If one of the affected holders of an NDA seeks review in a court of appeals, the me-too manufacturer can intervene; if not, he can bring his own action for judicial review in a district court. The me-too manufacturer is, of course, also given full opportunity to participate in the administrative proceedings considering possible withdrawal of approval for the NDA. See our *Bentex* brief at p. 21.

the drug at any time between 1938 and 1962 was a "new drug," which status would be evidenced by the fact that some member of the generic class had obtained an NDA.[33] On the other hand, if the drug, viewed generically, had never been a "new drug," then no manufacturer's example of it would have been the subject of an effective application, and it would clearly have been, in the words of Senator Eastland (*supra*, p. 25), "an established drug which [had] never been required to go through the new drug procedures."

Petitioner's assumption that this construction gives no meaningful independent content to Section 107(c)(4) is perhaps due to its understandable focus on prescription drugs, into which category bioflavonoids fall. In Section 503(b), Congress identified a class of drugs which could be dispensed only upon a physician's prescription. Prescription drugs include any drug for human use which (A) is habit-forming; (B) "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the professional supervision of a practitioner licensed by law to administer such drug"; or (C) is limited to prescription use in the application under Section 505. Given the character of these drugs, it is indeed most unlikely that any could have come on the market subsequent to 1938 without being a "new drug" for some period of time.

[33] As pointed out in our brief in *Bentex* (p. 6), FDA early adopted the practice of turning back an application if it appeared that the product in question was not a new drug.

But the same is not true of over-the-counter drugs, which cover a broad range from cough drops and mouthwash to aspirin, skin ointments, and cold remedies. Many of these products consist entirely of ingredients long known to be safe or demonstrably without any significant biological or chemical activity (others, however, have in fact required and obtained NDAs). Such products, coming on the market for the first time between 1938 and 1962 but consisting of old, established ingredients, might well never have been subject to new drug regulation. They would, accordingly, be entitled to the exemption conferred by Section 107(c)(4) from efficacy regulation under the new drug procedures, so long as their composition and labeling remains unchanged.[34]

These exempted products would not necessarily have been "grandfathered" under the 1938 Act. If, for example, aspirin had been newly proclaimed after 1938 as a remedy for acne, this would have constituted a new labeling representation that would have permitted it to be deemed a "new drug" with respect to that claimed use under Section 201(p). Unless, however, the labeling recommended some increased dosage above the amounts specified and accepted for other uses of the drug, no safety question would have arisen and aspirin-for-acne would not in fact have been subject

[34] This is not to say that they would be generally immune from removal from the market for inefficacy, only that such removal would not be pursuant to new drug regulation. Such products would be subject to removal for misbranding if ineffective for their claimed uses, and they are considered by FDA to be subject for this reason to the procedures it has established for regulation of over-the-counter drugs by rulemaking, described in our *Bentex* brief (pp. 24–25).

to "new drug" regulation. Section 107(c)(4) would thus confer upon aspirin an exemption from "new drug" regulation for efficacy that was not available to it under Section 201(p).[35]

This approach is wholly consonant with what can be gleaned of the congressional intent from the legislative history. As indicated in our discussion of that history (p. 28, *supra*), Senator Kefauver, the principal sponsor of the 1962 Amendments, commented upon the bill's failure to subject "proprietaries now on the market" to the requirement that they support their claims for effectiveness. This statement came in the context of a comparison of the bill's impact on proprietary and prescription drugs, from which it may reasonably be inferred that he considered the latter to be subject to the effectiveness provisions.[36] Moreover, in light of Section 503's delineation of standards for prescription drugs, it may be presumed that Congress was aware that such drugs were very likely to have been at one time "subject to the new-drug procedure," while the comparatively less dangerous proprietaries were not as likely to have been so subject.

In short, petitioner points to no reason of public

[35] Any change in labeling after October 10, 1962, would, of course, subject the entire product to the 1962 Amendments. See *United States* v. *Allan Drug Corporation*, 357 F. 2d 713 (C.A. 10), certiorari denied, 385 U.S. 899.

[36] And in their separate statement of views attached to Part 1 of the Senate Report, Senators Dirksen and Hruska spoke approvingly of the exclusion from efficacy regulation of drugs that "are as familiar in the family medicine chest as aspirin or epsom salts" (p. 61), thus corroborating our view of the kinds of products Congress considered worthy of exemption and thought it was exempting.

policy or equity to support its position that it and other "me-too" manufacturers should be permitted to go on marketing drugs without demonstrating by adequately controlled scientific studies that they are effective as claimed. There is, by contrast, every reason to apply the effectiveness requirements of the 1962 Amendments to such drugs if the Amendments are meaningfully to achieve their basic purpose.

CONCLUSION

For the reasons stated, the judgment of the court of appeals should be affirmed on the grounds specified in this brief.

Respectfully submitted.

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APRIL 1973.

APPENDIX

This Appendix sets forth the findings reported by the NAS–NRC panels on USV's bioflavonoid products, which were reviewed by the Panel on Drugs Used in Hematologic Disorders and/or the Panel on Drugs Used in Metabolic Disorders. Reproduced here is the report of the former on "C.V.P. with Vitamin K" and of the latter on "Duo-C.V.P." Also reproduced is the report of the Panel on Drugs Used in Hematologic Disorders relating to Parke, Davis & Company's product "Rutin," a prominent bioflavonoid compound; this report contains additional observations regarding the panel's conclusions about the effectiveness of bioflavonoids.

C.V.P. With Vitamin K, NDA 9965, Log 734

PANEL ON DRUGS USED IN HEMATOLOGIC DISORDERS

INDICATIONS:

I. As a supplementary source of bioflavonoids, ascorbic acid, and menadione.

EVALUATION: Ineffective.

COMMENTS: The label correctly states that the dietary need for these agents has not been established, in agreement with Burns.

DOCUMENTATION:

1. Burns, J. J. Water-soluble vitamins; II. ascorbic acid (vitamin C), pp. 1673–1680. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

Approved by William H. Crosby,
Chairman.

DUO-C.V.P., NDA 9965, Log 733

PANEL ON DRUGS USED IN METABOLIC DISORDERS

INDICATIONS

None.

GENERAL COMMENTS

I. There is no package insert, but just a label indicating that this is a "supplementary source of bioflavonoids and ascorbic acid." There is no definite claim for therapeutic use and a statement on the label admits that "the need for bioflavonoids in human nutrition has not been established." However, the inference is that there is indeed a need for such a product. The references support this inference, in that everything from threatened abortion to bleeding gums is reported to have responded. The use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved. The Panel recommends that there should be a clear statement as to the use of this preparation.

II. The Panel finds that the term "minimum daily adult" requirement is meaningless because variations in nutritional needs depend on the health, sex, age, and physical activity of the individual. The term "dietary allowances" is preferred.

III. See the general statement on multiple-vitamin preparations.

Approved by D. H. NELSON,
Chairman.

RUTIN, NDA 6132, LOG 2407

PANEL ON DRUGS USED IN HEMATOLOGIC DISORDERS

INDICATIONS

I. Capillary permeability.

EVALUATION: Ineffective.

COMMENTS: Capillary permeability is normal, and should not be abolished. Moreover, data documenting bioflavonoid deficiency in man or supporting beneficial effects of this compound in bleeding states are insufficient to establish any clinical value for preparations containing rutin or allied compounds. The clinical value claimed in the literature is based on uncontrolled observations or poorly evaluated case reports. Any positive effects encountered may well have represented an unsuspected action of concurrently administered ascorbic acid. In 1955, a symposium was conducted on this subject at the New York Academy of Sciences, and Youmans, in his summarizing remarks, concluded on the evidence of the hemostatic value of the bioflavonoids: ". . . unfortunately, for one reason or another, they do not prove it, nor provide evidence of it." (2) A similar view is held by Burns, who states: "Proof that flavonoids are useful therapeutic agents is far from conclusive." (1)

DOCUMENTATION:

1. Burns, J. J. Water-soluble vitamins; II. ascorbic acid (vitamin C), pp. 1673–1680. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

2. Youmans, J. B. Summary of the clinical aspects of bioflavonoids and ascorbic acid. Ann. N.Y. Acad. Sci. 61:729–731, 1955.

Approved by WILLIAM H. CROSBY,
Chairman.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-414

HYNSON, WESTCOTT & DUNNING, INCORPORATED,
Cross-Petitioner,

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

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REPLY BRIEF OF CROSS-PETITIONER HYNSON, WESTCOTT & DUNNING, INCORPORATED

ARGUMENT

I

The Existence Of Published Adequate And Well-Controlled Studies As A Prerequisite To A Finding Of General Recognition Of Safety And Effectiveness.

The Government contends that a showing of substantial evidence of effectiveness as defined in Section 505(d) of the Act is a condition precedent to a finding by experts under Section 201(p) that a drug is generally recognized as safe and effective and, therefore, not a new drug. We have shown in our main brief in this case (No. 72-414, pp. 21-28) that this proposed judicial amendment of the Act should be rejected. The legislative history and judicial precedent (Br. 15-19) and the

medical discourse on the necessity for controlled studies cited by the Government (App. A) do not support its position.

A. Legislative History.

The Government's recitation of testimony given at congressional hearings leading up to enactment of the Drug Amendments of 1962, is irrelevant. The interest of Congress and the experts testifying was in the type of evidence which the drug industry should be required to produce before a *new drug* should be permitted to be marketed. They were concerned with the marketing of new drugs without prior proof of effectiveness based upon adequate testing. We agree that Congress obviously intended that new drugs not be marketed without submission of substantial evidence as defined in Section 505 (d).

The question involved here, however, is not what type of evidence is required to prove the actual effectiveness of a new drug under Section 505 of the Act, but what evidence is required in order to bring a product within the new drug provisions of the Act, *i.e.*, evidence on the question of whether a drug is generally recognized as safe and effective under Section 201(p). The legislative history referred to in the Government's brief was not directed to this question and is, therefore, irrelevant.

B. The Cases Cited By The Government.

In its main brief in this case (No. 72-414), Hynson, Westcott & Dunning, Incorporated (HW&D) shows that the Government's attempt to graft the substantial evidence of effectiveness requirement in Section 505(d) to the jurisdictional test of new drug status in Section 201 (p) runs counter to a principle long-established in the case law: the question involved in determining whether

a drug is a new drug under Section 201(p) is not whether the drug is actually safe and effective but whether the drug is generally recognized as safe and effective by qualified experts (Br. 25-28).

The Government dismisses the authorities relied on by HW&D in a footnote in its brief (p. 23) and cites cases purporting to sustain its position. In actuality, the cases support HW&D's contention rather than the Government's. In each case the court pointed out that the question before it was not whether the drug *is* safe and effective, but whether it is generally recognized as safe and effective. *United States* v. *An Article Of Drug "Bentex Ulcerine"*, 469 F.2d 875, 879 (5th Cir. 1972); *United States* v. *41 Cases, More or Less*, 420 F.2d 1126, 1129 (5th Cir. 1970); *United States* v. *Article of Drug, Etc.*, 415 F.2d 390 (5th Cir. 1969), affirming 294 F. Supp. 1307, 1310 (D.Ga. 1968); *United States* v. *Article Of Drug . . . Mykocert*, 345 F.Supp. 571, 574 (D.Ill. 1972). The court in the case specifically relied on by the Government as supporting its position stated:

> "The statutory test for determining whether a drug is a "new drug" under 21 U.S.C. § 321(p) is whether the composition of the drug is generally recognized among experts qualified by their scientific training and experience to evaluate the safety and effectiveness of drugs as safe and effective for the uses prescribed, recommended or suggested in its labeling." *United States* v. *An Article of Drug . . . Xerac*, CCH Food, Drug, Cosmetic Law Reporter, ¶ 40,836 (No. 70-C-106, N.D. Ill.)

In any event, no court in any of the cases cited even mentioned the lack of substantial evidence test in Section 505(d) in connection with the general recognition test in Section 201(p). It is also significant to note that, as contrasted with the situation in the case at bar, litera-

ture on the drugs involved in the cases cited by the Government was either "virtually nonexistent" or completely lacking. *E.g., United States* v. *Article of Drug . . . Mykocert,* 345 F.Supp. 571, 575 (D.Ill. 1972). If Congress had intended that the substantial evidence test be read into Section 201(p), it could easily have said so.

II

The Right To A Hearing On The Question Of General Recognition Of Safety And Effectiveness.

The Government in its brief (No. 72-414) limits its argument to two questions, *viz.*, (1) whether substantial evidence of effectiveness in the medical literature consisting of adequate and well-controlled studies referred to in Section 505 (d) of the Act must exist before experts can determine if a drug is generally recognized as safe and effective within the meaning of Section 201 (p) of the Act; and (2) whether HW&D's drug, Lutrexin, is entitled to exemption from the effectiveness requirements of the Drug Amendments of 1962 by virtue of Section 107 (c) (4) thereof (Br. 8).

The Government thus completely ignores a basic contention of HW&D set forth in its main brief: assuming, *arguendo,* that substantial evidence of effectiveness as defined in Section 505(d) must be shown to exist in order to form a basis for experts to determine a drug to be generally recognized as safe and effective,[1] HW&D's affidavits and medical data (J.A. 32-72; 86-172), together with FDA's criticisms of them (J.A. 72), clearly show the existence of disputed issues of fact which, under fundamental principles of fairness and due process, should be resolved at a hearing (HW&D Br. in No. 72-414, 31-38).

[1] We show in Point I, *supra* and showed in our main brief (pp. 21-28), that this theory is not supported by the statute, its legislative history or judicial precedent.

The analysis of the affidavits and medical studies in our brief in No. 72-394 (pp. 14-25) further demonstrates that the evidence submitted to FDA in HW&D's request for a hearing (J.A. 24) raised genuine issues of fact as to whether HW&D has shown the existence of substantial evidence of effectiveness as defined in Section 505 (d) and as interpreted by FDA in its regulations (J.A. 487, 21 CFR 130. 12(a)(5)). The Government's statement (Br. 8) that HW&D ". . . contends that it is entitled to establish general recognition of safety and effectiveness under Section 201 (p) by means of evidence that would not suffice to satisfy the requirement of Section 505 . . ." is, therefore, clearly erroneous. HW&D's evidence cannot be dismissed as "uncontrolled clinical impressions" (Br. 13). The Government has made no attempt in its brief to refute HW&D's showing that its evidence raises disputed issue of adjudicative fact requiring a hearing. See *Goldberg* v. *Kelly*, 397 U.S. 254, 269-270 (1970).

HW&D is, therefore, entitled to a hearing on the new-drug status of Lutrexin and on the claims to exemption under 107(c) of the Drug Amendments of 1962. HW&D's affidavits and medical studies raise genuine issues of fact concerning the new-drug question and the exemption.[2]

III

Section 107(c) Of The 1962 Amendments.

A. The "Deemed Approved" Provision Of Section 107(c)(2).

The Government states that an NDA must remain "effective" even after the drug ceases to be "new" in order that FDA can retain the power to deal administratively with the contingency that doubt is cast upon the

[2] The status of HW&D's drug Lutrexin under FDA's "summary judgment" regulations is discussed in our brief in 72-394.

safety of a drug previously considered safe (Br. 27). We confess to bewilderment at this contention. If the Government were correct in its claim that an NDA remains "effective" even after the drug is no longer new and a question as to the safety of the drug should arise, the order withdrawing approval of the NDA could only be enforced by FDA in a judicial proceeding. This is precisely what FDA would have to do in order to challenge the safety of Lutrexin if our position is correct that, since Lutrexin was no longer "new" on October 9, 1962, its NDA was not "effective" on that date. There is no more reason for a continuing authority to withdraw an NDA for a drug which is no longer "new" than there is for such authority with respect to a drug which was never NDA'd because it was once generally recognized as safe but later was judged by FDA to be, in fact, not safe, upon the basis of new evidence.

Since no NDA for Lutrexin was "effective" on October 9, 1962, the drug was not "deemed approved." (For the same reason it was not covered by an "effective" application within the meaning of Section 107 (c) (4) (C)).

The Government refers to the provision of Section 107 (c) (2) that applications effective on October 9, 1962 would be "deemed approved", as a mere housekeeping measure." In our main brief (pp. 38-41), we discuss the meaning of this provision. We doubt that the use of a word so intimately linked to new drug procedures as is "effective", would be employed by the Congress as no more than a housekeeping device. Thus, an NDA for a new drug must be "effective" before the drug can legally be marketed. The term obviously has more meaning than the Government would give it.

It is also said by the Government that, if Lutrexin were not "deemed approved" the marketing of the drug would have been illegal since it could not claim approved

status under Section 107 (c) (2) and (3). On the contrary, it seems clear that only drugs "deemed approved" are subject to administrative withdrawal proceedings under either Section 107 (c) (3) or Section 505. Concededly, Lutrexin, though not "deemed approved," would be subject to the institution of judicial proceedings on the ground, *e.g.*, that it is a new drug because it is not generally recognized as effective. Only if it is also exempt under Section 107 (c) (4) would it be protected against a claim that it was a new drug without an approved application.

B. Section 107(c)(4).

The Government says that, despite the argument to the contrary in our main brief (p. 44), its interpretation of Clause (C) does, indeed, permit the exemption of over-the-counter drugs which, "as a generic class," were never subject to new drug regulations, even though they came on the market between 1938 and 1962, "because of universal recognition of the safety of their old, established ingredients" (Br. 27).

In its brief in *USV* (No. 72-666) the Government is less firm about the status of such drugs. It there states that such products "might well have never been subject to new drug regulation" (p. 51). This seems a more accurate suggestion as to the status of such products, particularly in the light of the new drug regulations of FDA which contemplate that almost any change in the active or inactive ingredients of a drug, or new combination of non-new drug ingredients, or new uses, or new dosages, may cause a drug to be "new".[3]

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[3] The pertinent provisions of the regulations follow (21 CFR 130.1)—

(h) The newness of a drug may arise by reason (among other reasons) of:

(1) The newness for drug use of any substance which composes such drug, in whole or in part, whether it be

The Government's argument does not square with the provision of Section 130.1(h)(4) relating to new uses of drugs which are not new drugs when promoted for other uses. This regulation reflects a long-standing policy of FDA which was followed before the enactment of the effectiveness provisions of the 1962 Amendments.[4] It seems clear that any new combination of "old" ingredients would be subject to new drug procedures, even before 1962, as well as any new use or dosage and would continue to be so subject until they became generally recognized as safe and had been used to a material extent and for a material time. The Government has not, we submit, substantiated its argument that it has not, in effect, read Section 107(c)(4) out of the 1962 Amendments.

Nor is there any evidence that the addition of the requirement of effectiveness to Section 201(p) elim-

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an active substance or a menstruum, excipient, carrier, coating, or other component.

(2) The newness for drug use of a combination of two or more substances, none of which is a new drug.

(3) The newness for drug use of the proportion of a substance in a combination, even though such combination containing such substance in other proportion is not a new drug.

(4) The newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body.

(5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.

[4] The provision relating to newness of drugs including new uses of old drugs was in effect in 1956, long before effectiveness requirements were added in 1962. See Section 130.1(f)(4) of 21 CFR, revised as of January 1, 1963.

inated a Section 107(c)(4) exemption for Lutrexin, as the Government contends (Br. 23 et seq.). It must be remembered that Section 107(c)(4) was not in S.1552 when it was first reported to the Senate before the addition of "effectiveness" to Section 201(p).[5] It is, therefore, not apparent how, as the Government states, Lutrexin could have been "grandfathered" without the transitional provisions, including Section 107(c)(4), had been adopted. In any event, that section should be interpreted on the basis of the statute as enacted, and not, as the Government would have it, on the basis of different provisions in an earlier bill.

The addition of "effectiveness" to Section 201(p) was hardly as significant, in this connection, as the Government suggests. The basis assigned for such addition was "to eliminate any possible ambiguity" on the question "as to the circumstances and extent to which a new claim or change of claim for effectiveness made after the initial approval of a new drug application could be made without supporting evidence to be submitted to the Department under the new drug procedure."[6]

We submit, therefore, that in view of this expression of the Senate Committee and the discussion in our main brief, the Government is wrong when it states "this history thus establishes that Congress abandoned its original inclination to exempt 'safe' pre-1962 drugs from the new drug effectiveness requirements . . ." (Br. 31).

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[5] S. Rep. 1744, Part 2, 87th Cong., 2nd Sess., p. 7.

[6] *Id.* at 5.

CONCLUSION

For the foregoing reasons and the reasons stated in our brief in No. 72-394 and in our main brief in this case (No. 72-414), (1) the decision of the Court of Appeals that HW&D was entitled to a hearing on the question of whether there is substantial evidence of effectiveness of Lutrexin should be affirmed; (2) the NDA for Lutrexin was not "deemed approved" under the provisions of Section 107(c)(2) of the Drug Amendments of 1962 and was therefore not subject to *administrative* withdrawal proceedings under Section 505(e)(3) of the Act as amended; (3) the drug is entitled to the exemption from *any* proceedings based on the *effectiveness* requirements of the 1962 Amendments by reason of Section 107(c)(4); and (4) HW&D is entitled to an evidentiary hearing before FDA on the jurisdictional questions of whether Lutrexin was "deemed approved" and therefore not subject to administrative withdrawal proceedings under Section 505(e)(3), whether it was exempt under Section 107(c)(4), and whether it is now generally recognized as both safe and effective and not subject to Section 505.

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